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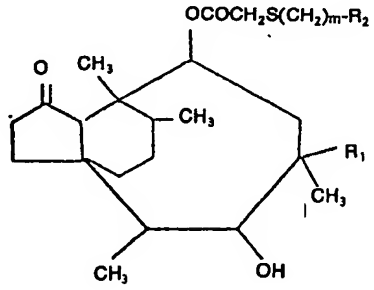
(54) New pleuromutilin derivatives, their production and use.

(57) Novel pleuromutilin derivatives of formula I,



I

in which
R_1 is ethyl or vinyl,
m is 0 or 1, and
R_2 is a heterocyclic radical, in which a 5- or 6-membered, unsaturated or saturated heterocyclic ring containing one or more hetero atoms selected from oxygen, sulphur and nitrogen, is attached to the $-S(CH_2)_m$-group, provided that when n is 0, R_2 is other than pyridyl,
their production and use as antimicrobial agents are described.

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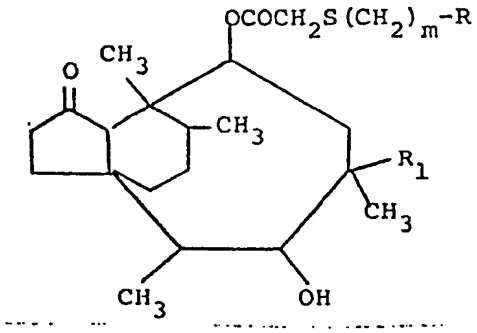
NEW PLEUROMUTILIN DERIVATIVES, THEIR PRODUCTION AND USE

This invention provides compounds of formula I,



I

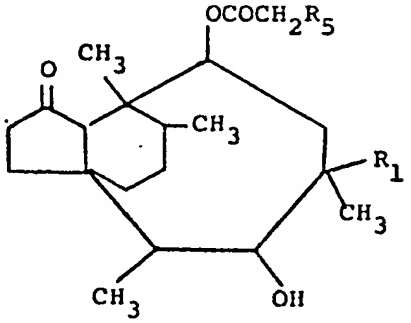
in which R_1 is ethyl or vinyl,

m is 0 or 1, and

R_2 is a heterocyclic radical, in which a 5- or 6-membered, unsaturated or saturated heterocyclic ring containing one or more hetero atoms selected from oxygen, sulphur and nitrogen, is attached to the $-S(CH_2)_m-$ group,

provided that when m is 0, R_2 is other than pyridyl.

The invention also provides a process for the production of compounds of formula I, characterised by reacting a compound of formula II,



II

in which R_1 is as defined above, and

R_5 is chlorine, bromine or $-OSO_2R_7$, in which R_7 is alkyl or aryl,

with a compound of formula III,

$$HS-(CH_2)_m-R_2 \qquad III$$

in which m and R_2 are as defined above.

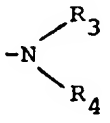
The process is suitably carried out in the presence of an alkali metal lower alkoxide, for example sodium ethoxide or methoxide. This is preferably produced in situ. Conveniently, the compound of formula III may be dissolved in a solution of sodium in a water-free lower alkanol, e.g. methanol or ethanol. A solution of the compound of formula II in an inert organic solvent, e.g. an aliphatic ketone, such as methyl ethyl ketone or acetone, is then conveniently added. The process is suitably effected at a temperature from room temperature to the

reflux temperature of the reaction mixture, in particular from 22° to 55°C. The reaction time may typically vary from 2 to 12 hours.

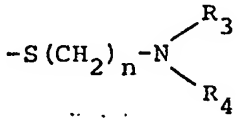
The resulting compounds of formula I may be isolated and purified using conventional techniques. Where required, free base forms thereof may be converted into salt forms, in particular into acid addition salt and quaternary ammonium salt forms, in conventional manner, and vice versa.

R_2 suitably signifies a 5- or 6-membered saturated or unsaturated heterocyclic ring containing one or more hetero atoms selected from oxygen, sulphur and nitrogen. The ring may be unsubstituted. Alternatively, it may be mono- or poly-substituted. Suitable substituents include mercapto, thioxo, hydroxy, lower alkyl, lower alkanoyl, lower sulfoxyl, nitro, lower alkylsulphonyl, trifluoromethyl, formyl, lower alkoxycarbonyl, lower hydroxyalkyl, lower dihydroxyalkyl and halogen.

Further suitable substituents are of formulae II, III and IV,

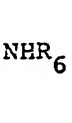


II



III

and



IV

in which either R_3 and R_4 are the same or different and each is hydrogen, lower hydroxyalkyl, lower dihydroxyalkyl, unsubstituted or substituted lower alkanoyl, lower alkyl sulfonyl or lower alkyl,
or R_3 and R_4 together with the nitrogen atom form a piperazinyl radical, which may be substituted on the second nitrogen atom by lower alkyl, lower hydroxyalkyl or lower dihydroxyalkyl,
n is 2 to 5,
X is oxygen or sulphur,
and R_6 is lower alkyl or lower alkocycarbonyl.

Other substituents include further 5- or 6-membered, saturated or unsaturated heterocyclic rings, e.g. pyridyl, which may themselves be unsubstituted or mono- or poly-substituted as described above.

Finally, the heterocyclic ring of R_2 may suitably be fused to one or more 5- or 6-membered, saturated or unsaturated carbocyclic or heterocyclic, preferably carbocyclic, e.g. benzene, rings. This ring may also be unsubstituted or similarly mono- or poly-substituted, as described above.

As used herein, the term "lower" signifies preferably of 1 to 4, more preferably 1 to 2 carbon atoms. "Halogen" signifies chlorine, bromine, fluorine or iodine, prefer-

ably chlorine, bromine or fluorine, more preferably chlorine.

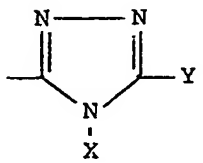
The preferred heterocyclic rings in R_2 linked to the $-S(CH_2)_m-$ radical contain one or more hetero atoms selected from nitrogen and sulphur. The more preferred ring contains at least one nitrogen atom.

One group of such hetero rings may contain nitrogen as the sole hetero atom, in particular 1, 2 or 3 nitrogen hetero atoms. Suitable 5- or 6-membered hetero rings containing a single nitrogen atom include pyridine (when m is 1), pyrrole and 4,5-dihydro-3H-pyrrole. Suitable 5- or 6-membered rings containing 2 nitrogen atoms include imidazole, pyridazine, pyrimidine. Such rings may be fused to, e.g. one or more benzene rings, e.g. to form benzimidazole or perimidine. Suitable 5- or 6-membered hetero rings containing 3 nitrogen atoms include 1,2,4-triazole.

Another group of hetero rings may contain 1 nitrogen atom and 1 sulphur atom, e.g. thiazole, 4,5-dihydrothiazole and benzothiazole. Another group of hetero rings contain 2 nitrogen and 1 sulphur atom, e.g. 1,3,4-thiadiazole.

Preferred compounds are those in which the heterocyclic ring of R_2 is bound to the $-S-(CH_2)_m-$ group via a ring carbon atom. Particularly preferred compounds are those in which the hetero ring of R_2 is 1,2,4-triazole.

A particularly preferred group of compounds are those in which R_2 is formula V,



V

in which X is hydrogen, lower alkylsulphonyl, amino, a group of formula II, III or IV; formyl, and Y is hydrogen, amino, trifluoromethyl, lower alkyl, a group of formula II, or pyridyl.

The compounds of formula I are indicated for use as chemotherapeutic agents, in particular as antimcrobial agents, as indicated, e.g. by their inhibiting effect against various bacterial strains, e.g. Staph. aureus, Staph. epidermis, Strept. pyogenes, Strept. aranson, Strept. pneumoniae, Strept. faecelis, Strept. viridans, Corynebact. pyogenes, Sarcina lutea, Klebsiella pneumoniae, and Haemophilus influenzae, in vitro in the series dilution test at a concentration, for example, of 0.01 to 25 µg/ml, and in in vivo tests in mice. The compounds also show an inhibiting effect against various mycoplasma, e.g. M. hominis, M. arthritidis, M.. pneumoniae, and urea plasma urealyticum, and chlamydia, in vitro in the series dilution test at concentrations of, for example, 0.008 to 2.5 µg/ml.

The compounds also show an inhibiting effect against various obligatory anaerobes, e.g. Bacteroides fragilis, Bacteroides melaninogenicus, Sphaerophorus necrophorus, Clostridium perfringens, etc., in vitro in the series dilution test at concentrations of for example 0.1 to 4 ug/ml, and in vivo in mice at a dosage of for example 50 to 200 mg/kg of animal body weight, p.o or s.c.

The compounds are therefore indicated for use as antimicrobial agents, in particular as antibacterially active antibiotics and for treatment of infections caused by obligatory anaerobes.

For the above-mentioned uses, an indicated suitable daily dosage is from about 1 to 3 g, suitably administered in divided dosages of from two to four times daily, or in retard form.

The compounds alone or in admixture with a tetracyclin may be administered orally or parenterally in such forms as tablets, capsules, powders, granulates, and injectable or

infusion preparations, e.g. solutions or suspensions. The compounds may also be employed in the form of creams or tinctures. For veterinary purposes, the compounds may also be administered as food or drink additives.

It has also been found that mixtures of the compounds of formula I with a tetracyclin with R-factor coded tetracyclin resistence show a synergistic antibacterial effect against resistent strains of this type. This indicated for example by determination of the minimum inhibition concentration of the mixture and the individual components in the series dilution test, and by evaluating the results by the method of Löwe (isobole diagram), Die Antibiotika, Volume 1, part 1, 65ff, 1962. Conventional tetracyclines, e.g. chlorotetracyclin, oxytetracyclin, demethyltetracyclin, tetracyclin dioxycyclin, monocyclin, metacyclin, and rolitetracyclin, may be employed in such mixtures. The quantity of the compound of formula I in such mixtures is suitably 10 to 90%, preferably 20 to 35%, in particular 25%, while the quantity of the tetracyclin is suitably from 90 to 10%, preferably 80 to 65%, particularly 75% (these percentages being by weight).

The mixtures are particularly indicated in treating infections of the gastrointestinal tract and other local infections of the organ.

The compounds of formula I, when used alone or in admixture with a tetracyclin, may be employed in free base form or in the form of chemotherapeutically acceptable acid addition or quaternary ammonium salts. These salt forms have the same order of activity as the free base forms.

Suitable acid addition salt forms include the hydrochloride, hydrogen fumarate, fumarate and naphthalene-1,5-sulphonate.

The compounds (or mixtures thereof with a tetracycline) may be admixed with a chemotherapeutically acceptable diluent or carrier and, optionally other conventional excipients for the production of galenic forms. Suitable excipients include sweeteners, aromas, colouring agents, preserving agents, e.g. ethyl-o-hydroxybenzoate, fillers or carriers, e.g. diluents, such as calcium carbonate, disintegrating agents, e.g. starch or alginic acid, binding agents, e.g. starch, gelatine or acacia, and lubricating agents, e.g. magnesium stearate, stearic acid or talc. Oral liquid forms may contain conventional suspending agents, e.g. methylcellulose, tragacanth or sodium alginate. Suitable wetting agents include lecithin, polyoxyethane stearate and polyoxyethylene sorbitan monooleate. For the production of capsules, suitable diluents include calcium carbonate, calcium phosphate and kaolin.

The preferred compound of formula I is that of Example 1, hereinafter.

The following Examples illustrate the invention. All temperatures are in degrees Centigrade.

EXAMPLE 1: 19,20-Dihydro-14-O-[(3-amino-1,2,4-triazol-5-yl)thioacetyl]mutilin

2.3 g of sodium are taken up in 500 ml of absolute ethanol. After formation of the sodium ethoxide, 11.6 g of 3-amino-5-mercapto-1,2,4-triazol are added to the solution.

The mixture is allowed to react for 3 hours at 25° and is then mixed with a solution of 53.5 g of 19,20-dihydro-22-O-tosyl-pleuromutilin in 200 ml of ethylmethylketone. The homogenous reaction mixture is held for 12 hours at 25° and then poured onto water and extracted 3 times with 500 ml of ethyl acetate. The purified ethyl acetate extract is shaken with water, dried over Na_2SO_4 and evaporated in vacuo. The crude product is chromatographed over silica gel (eluant: ethyl acetate) to obtain the heading compound, m.p. 213-215° (isopropanol/H_2O).

NMR (DMSO): 5.76 (broad, 2H, NH_2); 5.52 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz);
3.76 (s, 2H, S-CH_2-CO); 3.35 (m, 1H, H_{11}).

IR (-KBr): 2600-3600 (broad), 1720, 1635, 1280 cm^{-1}.

The compounds of the following Examples may be produced in manner analogous to that of Example 1, using appropriate starting materials in approximately equivalent amounts.

Example 2: 14-O-[3 Amino-1,2,4-triazol-5-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): 5.68 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.34 (d, 1H, H_{11}, $J_{H_{11}H_{10}}$ = 6 Hz); 3.7 (s, 2H, S-CH_2-CO); 5.26-4.95 (m, 4H, NH_2 + $2H_{20}$); 6.5-6.16 (m, 1H, H_{19}).

IR (KBr): 3300 (broad), 1720, 1625, 1575, 1270 cm^{-1}.

EXAMPLE 3: 14-O-[(Imidazol-2-yl)thioacetyl]mutilin

NMR ($CDCl_3$/DMSO 5:1): 6.98 (s, 2H, Imidazol H); 5.65 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.76 (s, 2H, S-CH_2CO); 3.4-3.2 (m, 1H, H_{11}).

IR (KBr): 3600-2600 (broad), 1730, 1705, 1270 cm^{-1}.

EXAMPLE 4: 14-O[(Perimidin-2-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 7.0-7.2 (m, 4H, arom. H); 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.72 (AB-System, 2H, S-CH_2-CO, J=16.2 Hz); 3.42-3.22 (m, 1H, H_{11}).

IR (KBr): 3600-3100 (broad), 1720, 1625, 1585, 1270, 820, 770 cm^{-1}.

EXAMPLE 5: 14-O-[(4,5-Dihydro-3H-pyrrol-2-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz), 3.96-3.58 (m, 4H, 2-Pyrrolidin H + S-CH_2-CO); 3.36 (dd, 1H, H_{11}, J=6.3 Hz, J=10.8 Hz).

IR ($CHCl_3$): 1720, 1590 cm^{-1}.

EXAMPLE 6: 14-O-[(Benzimidazol-2-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 7.5-7.0 (m,4H, arom. H); 5.64 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8.2 Hz); 4.1 (s, 2H, S-CH_2-CO); 3.38 (d, 1H, H_{11}, $J_{H_{11}H_{10}}$ = 6.3 Hz).

IR (KBr): 3550-2600 (breit), 1720, 1270, 740 cm^{-1}.

EXAMPLE 7: 14-O-[(4-Methylsulfonyl-5-amino-1,2,4-triazol-3-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 5.9 (s, 2H, NH_2); 5.76 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.81 (s, 2H, S-CH_2-CO); 3.3 (s, 3H, CH_3SO_2-); 3.4 (m, 1H H_{11}).

IR (KBr): 3400 (broad), 1720, 1625, 1265, 1275, 1180 cm^{-1}.

EXAMPLE 8: 14-O-[(3-Mercaptopyridazin-6-yl)thioacetyl]-19,20-dihydromutilin

NMR ($CDCl_3$): 7.5 (d, 1H, arom. H, J=9 Hz); 6.9 (d, 1H, arom. H, J=9 Hz); 5.64 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.79 (s, 2H, S-CH_2-CO); 3.44 (d, 1H, H_{11}, $J_{H_{11}H_{10}}$ = 6 Hz).

IR (KBr): 3400 (broad), 1720, 1270, 1155, 1140 cm^{-1}.

EXAMPLE 9: 14-O-[(2-Isopropyl-4-hydroxypyrimidin-6-yl)methylthioacetyl]mutilin

NMR ($CDCl_3$): 6.32 (s, 1H, arom. H); 5.81 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.62 (s, 2H, S-CH_2-CO); 3.3 (s, 2H, S-CH_2-Arom.); 3.4 (m, 1H, H_{11}).

IR (KBr): 3400 (broad), 1720, 1650, 1590, 1275 cm^{-1}.

EXAMPLE 10: 14-O-{[3-(4-Hydroxyäthylpiperazin-1-yl-äthylthio)pyridazin-6-yl]thioacetyl}mutilin hydrochloride form

NMR ($CDCl_3$/ CD_3OD 50:1): 7.26 (s, 2H, arom. H); 5.7 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz).

IR (KBr): 3350 (broad), 1720, 1380, 1270, 1140 cm^{-1}.

EXAMPLE 11: 14-O-[(6-Nitrobenzothiazol-2-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): 8.68 (d, 1H, arom. H, J=2.3 Hz); 8.3 (dd, 1H, arom.H, J_1=2.3 Hz, J_2=9 Hz); 7.84 (d, 1H, arom. H, J=9 Hz); 5.78 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); AB-System: (v_A=3.18, v_B=3.06, S-CH_2-CO, J=16.2 Hz); 3.34 (dd, 1H, H_{11}, J=6 Hz, J=10.8 Hz).

IR (KBr): 3400 (broad), 1720, 1510, 1325, 1265, 1010 cm^{-1}.

EXAMPLE 12: 14-O-[(4-Methyl-6-hydroxypyrimidin-2-yl)-thioacetyl]mutilin

NMR (DMSO): 5.94 (s, 1H, arom. H); 5.53 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.9 (s, 2H, S-CH_2CO); 3.4 (m, 1H, H_{11}); 2.14 (s, 3H, CH_3).

IR (KBr): 3400 (broad), 1720, 1650, 1525, 1270, 1160 cm^{-1}.

EXAMPLE 13: 14-O-[(4-Ethoxycarbonyl-3,5-dimethylpyrrol-2-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 8.75 (b, 1H, NH); 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 4.26 (q, 2H, -OCH_2CH_3); 3.22 (s, 2H, S-CH_2CO); 3.36 (dd, 1H, H_{11}, J=6.3 Hz, J=10.8 Hz); 2.46 (s, 3H, CH_3-Pyrrol); 2.28 (s, 3H, CH_3-Pyrrol).

IR (KBr): 3600-3200 (broad), 1720, 1780, 1250, 1100 cm^{-1}.

EXAMPLE 14: 14-O-[(1-Methylimidazol-2-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): 7.0 (d, 1H, Imidazole H, J=1.8 Hz); 6.86 (d, 1H, Imidazole H, J=1.8 Hz); 5.7 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.78 (s, 2H, S-CH_2CO); 3.62 (s, 3H, N-CH_3); 3.34 (m, 1H, H_{11}).

IR (KBr): 3200 (broad), 1720, 1270 cm^{-1}.

m.p.: 135-136°.

EXAMPLE 15: 14-O-[(3-Mercaptopyridazin-6-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): AB-System of the Pyridazinprotons (ν_A=7.5, ν_B=6.9, J_{AB}=9 Hz); 5.64 (1H, H_{14}, $J_{H_{14}H_{13}}$ = 7 Hz); 3.78 (s, 2H, S-CH_2-CO); 3.44 (1H, H_{11}, $J_{H_{11}H_{10}}$ = 6.3 Hz).

IR (KBr): 3400 broad (OH), 1725 (CO), 1140, 1155 cm^{-1}.

EXAMPLE 16: 14-O-[(3-Chlorpyridazin-6-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): 5.78 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.38 (m, 1H, H_{11}); 1.44 (s, 3H, $(CH_3)_{15}$); 1.21 (s, 3H, $(CH_3)_{18}$); AB-System of the Pyridazin-H (ν_A=7.29, ν_B=7.33, J_{AB}=9 Hz); AB-System $(CH_2)_{22}$ (ν_A=4.12, ν_B=4.02, J_{AB}=16 Hz).

IR (KBr): 3500 (OH), 1720 (CO) cm^{-1}.

EXAMPLE 17: 14-O-[(4,5-Dihydrothiazol-2-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): 5.75 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.81 (s, 2H, -$(CH_2)_{22}$-); 1.46 (s, 3H, $(CH_3)_{15}$); 1.17 (s, 3H, $(CH_3)_{18}$); 4.14 (t, 2H, -S-CH_2, J=8 Hz); 3.4 (t, 2H, =N-CH_2).

IR (KBr): 3500 (OH), 1710 (CO), 1570 cm^{-1}.

EXAMPLE 18: 14-O-[(3-Diethylaminoäthylthiopyridazin-6-yl)thioacetyl]mutilin hydrogen fumarate form

NMR ($CDCl_3$): 7.14 (s, 2H, Pyridazin-H); 5.78 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 4.1 (s, 2H, S-CH_2-CO); 3.4 (m, 3H, H_{11} und CH_2-N<); 2.9 (m, 2H, CH_2-S-); 2.66 (q, 4H, N-CH_2-CH_3); 1.1 (t, 6H, N-CH_2-CH_3); 1.46 (s, 3H, $(CH_3)_{15}$); 1.1 (s, 3H $(CH_3)_{18}$).

IR (KBr): 3400 (broad, OH), 1720 (CO), 1140 cm^{-1}.

EXAMPLE 19: 14-O-[(4-Amino-1,2,4-triazol-3-yl)-thioacetyl]mutilin

NMR ($CDCl_3$): 8.26 (s, 1H, Triazol-H); 5.7 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 5,08 (s, 2H,NH_2), AB-System (v_A = 3.86, v_B=3.75, J_{AB}=16.2 Hz, S-CH_2-O); 3,34 (dd, 1H, H_{11}, J=6.3 Hz, J=10.2 Hz).

IR (KBr): 3400 (broad), 1720 cm^{-1}.

EXAMPLE 20: 14-O-[(3-(4-Pyridyl)-1,2,4-triazol-5-yl)-thioacetyl]mutilinhydrochlorid

NMR (DMSO): 8.95 (d, 2H, Pyridin-H, J=6.3 Hz); 8.36 (d, 2H-Pyridin-H, J=6.3 Hz); 5.55 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 4.16 (s, 2H, S-CH_2-CO); 3.4 (d, 1H, H_{11}, $J_{H_{10}H_{11}}$ = 6.3 Hz).

IR (KBr): 3600-2500 (broad), 1725, 1635 cm^{-1}.

EXAMPLE 21: 14-O-[(4-Amino-3-trifluormethyl-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 5.18 (s, 2H, NH_2); 3.9 (s, 2H, S-CH_2CO); 3.38 (m, 1H, H_{11}).

IR (KBr): 3400 (broad), 1720, 1190, 1150 cm^{-1}.

EXAMPLE 22: 14-O-[(4-Amino-3-methyl-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 5.72 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 4.97 (s, 2H, NH_2); AB-System (v_A=3.84, v_B=3.69, J_{AB}=16.2 Hz, S-CH_2-CO); 3.38 (dd, H_{11}, J=6.3 Hz, J=10.2 Hz).

IR (KBr): 3400 (broad), 1725 cm^{-1}.

EXAMPLE 23: 14-O-[(3-Methyl-4-acetamido-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 5.7 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.8 (s, 2H, S-CH_2-CO); 3.38 (m, 1H, H_{11}); 2.33 (s, 3H, CH_3CO-N); 2.26 (s, 3H, Triazol-CH_3).

IR (KBr): 3400 (broad), 1720, 750 cm^{-1}.

EXAMPLE 24: 14-O[(3-(Methoxysulfonylethylcarboxamido)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 5.72 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.82

(s, 2H, S-CH_2-CO); 3.34 (m, 1H, H_{11}); 3.14 (s, 3H, -O-CH_3).

IR (KBr): 3400 (broad), 1720, 1625, 1550, 1305, 1110, 730 cm^{-1}.

EXAMPLE 25: 14-O-[(1-Ethylaminocarbonyl-3-amino-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$ / CD_3OD 10:1): 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.75 (s, 2H, S-CH_2-CO); 3.38 (q, 2H, CH_3-CH_2-N); 3.4 (m, 1H, H_{11}); 1.26 (t, 3H, CH_3-CH_2-N).

IR (KBr): 3540, 3430, 3310, 1710, 1630, 1300 cm^{-1}.

m.p.: 230-232°.

EXAMPLE 26: 14-O-[(3-Amino-4-formyl-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 8.52 (s, 1H, Formyl-H); 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.82 (s, 2H, S-CH_2CO); 3.36 (m, 1H, H_{11}).

IR (KBr): 3600-2800 (broad), 1725, 1585, 1290 cm^{-1}.

EXAMPLE 27: 14-O-{[3-Amino-1-(carbethoxythiocarbamyl)-1,2,4-triazol-5-yl]thioacetyl}mutilin

NMR ($CDCl_3$): 7.74 (b, 2H, NH_2); 5.81 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz);

4.37 (q, 2H, O-CH_2CH_3); 3.83 (s, 2H, S-CH_2-CO); 3.4 (d, 1H, H_{11}, $J_{H_{11}H_{10}}$ = 6.3 Hz); 1.38 (t, 3H, O-CH_2CH_3).

IR (KBr): 3300 (broad), 1770, 1725, 1635, 1465, 1185 cm^{-1}.

EXAMPLE 28: 14-O-[(3 Amino-4-(Ethylaminothiocarbonyl)-1,2,4-triazol-5-yl)thioacetyl]mutilin

NMR ($CDCl_3$): 8.56 (m, 1H, NH); 7.4 (b, 2H, NH_2); 5.76 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.78 (s, 2H, S-CH_2-CO); 3.68 (m, 2H, N-CH_2-CH_3); 3.38 (dd, 1H, H_{11}, J=6.3 Hz, J=10.2 Hz); 1.33 (t, 3H, N-CH_2-CH_3).

IR (KBr): 3340 (broad), 1720, 1630, 1290 cm^{-1}.

EXAMPLE 29: 14-O-{[4-Bis-(methylsulfonylamino)-1,2,4-triazol-3-yl]thioacetyl}mutilin

NMR ($CDCl_3$): 8.28 (s, 1H, Triazol-H); 5.72 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); AB-System (v_A=4.18, v_B= 4.02, J_{AB} = 16.2 Hz, S-CH_2-CO); 3.6 (s, 3H, CH_3SO_2-); 3.58 (s, 3H, CH_3SO_2-); 3.34 (m, 1H, H_{11}).

IR (KBr): 3450 (broad), 1720, 1380, 1160 cm^{-1}.

EXAMPLE 30: 14-O-[(Benzimidazol-2-yl-methyl)thioacetyl]-mutilinhydrochloride

NMR ($CDCl_3$): 7.6 (m, 2H, arom.H); 7.2 (m, 2H, arom.H);

5.8 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 4.07 (s, 2H, S-CH_2-Arom.); 3.42 (m, 1H, H_{11}); 3.25 (s, 2H, S-CH_2-CO).

IR (KBr): 3600-2700 (broad), 1720, 1270, 740 cm^{-1}.

EXAMPLE 31: 14-O-[(2-Methyl-4-hydroxypyrimidin-6-yl)-methylthioacetyl]mutilin

NMR ($CDCl_3$): 6.3 (s, 1H, NH); 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); 3.58 (s, 2H, S-CH_2-Arom.); 3.36 (m, 1H, H_{11}); 3.14 (s, 2H, S-CH_2-CO); 2.46 (s, 3H, Pyrimidin-CH_3).

IR (KBr): 3400 (broad), 1720, 1650, 1590, 1270, 1110 cm^{-1}.

EXAMPLE 32: 19,20-Dihydro-14-O-[(3-diethylaminoethyl-thiopyridazin-6-yl)thioacetyl]mutilin, fumarate form

NMR ($CDCl_3$): 7.14 (s, 2H, Pyridazin-H); 6.78 (s, 1H, Fumarsäure-H); 5.6 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz); AB-System (v_A=4.14, v_B=3.92, J_{AB}= 16.2 Hz); 2.97 (q, 4H, N-CH_2-CH_3); 1.23 (t, 6H, N-CH_2-CH_3); 3.6-3.1 (m, 4H, S-CH_2-CH_2-N<).

IR (KBr): 3400 (breit), 1720, 1385, 1140, 1110 cm^{-1}.

EXAMPLE 33: 14-O-{[3-(2-Pyridyl)-1,2,4-triazol-5-yl]-thioacetyl}mutilin

NMR ($CDCl_3$): 8.82 (d, 1H, Pyridin-H, J=5 Hz);

8.24 (d, 1H, Pyridin-H, J=10 Hz), 7.9 (m, 1H, Pyridin-H), 7.45 (m, 1H, Pyridin-H), 5.78 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8 Hz), 4.0 (s, 2H, S-CH_2-CO), 3.4 (m, 1H, H_{11}).

IR (KBr): 3500-2800 (broad), 1720, 1450, 1280 cm^{-1}.

UV (CH_3OH): 232 nm (ε = 12400), 282 (8170).

EXAMPLE 34: 14-O-[(2-Methyl-1,3,4-thiadiazol-5-yl)thioacetyl]-mutilin

NMR ($CDCl_3$): 5.78(d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8.1 Hz), 4.07 (s, 2H, CH_2-S-CO), 3.38 (dd, 1H, H_{11}, $J_{H_{11}H_{10}}$ = 6.3 Hz, $J_{H_{11}OH}$ = 10,8 Hz), 2.72 (s, 3H, CH_3-thiadiazol).

IR (KBr): 3400 (OH) (broad) 1730 (CO) cm^{-1}.

UV (CH_3OH): 264 nm (ε=5330).

EXAMPLE 35: 14-O[(2-Amino-1,3,4-thiadiazol-5-yl)thioacetyl]-mutilin

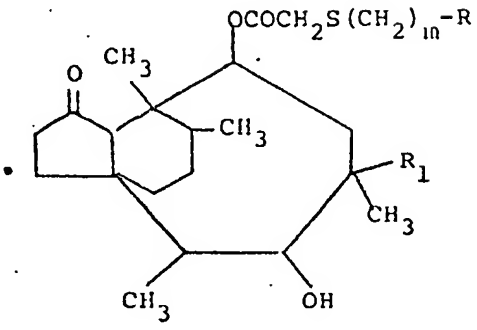
NMR ($CDCl_3$): 5.74 (d, 1H, H_{14}, $J_{H_{14}H_{13}}$ = 8.1 Hz), 5.32 (b, 2H, NH_2), 3.88 (s, 2H, S-CH_2-CO), 3.34 (m, 1H, H_{11}).

IR (KBr): 3400 (NH_2, OH), 1730 (CO) cm^{-1}.

UV (CH_3OH): 282 nm (ε=7150).

WHAT WE CLAIM IS:

1. A compound of formula I,



I

in which R_1 is ethyl or vinyl,

m is 0 or 1, and

R_2 is a heterocyclic radical, in which a 5- or 6-membered, unsaturated or saturated heterocyclic ring containing one or more hetero atoms selected from oxygen, sulphur and nitrogen, is attached to the $-S(CH_2)_m-$ group,

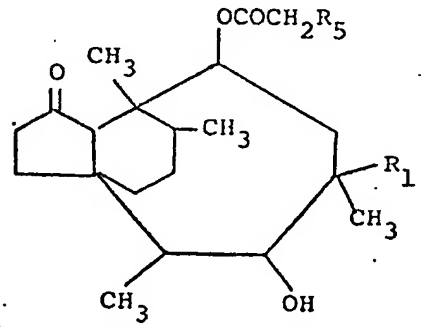
provided that when m is 0, R_2 is other than pyridyl,

and acid addition and quaternary ammonium salts thereof.

2. The compound of Claim 1, which is 19,20-dihydro-14-O-[(3-amino-1,2,4-triazol-5-yl)thioacetyl]mutilin.

3. A chemotherapeutic composition comprising a compound of Claim 1, in association with a chemotherapeutically acceptable diluent or carrier.

4. A process for the production of a compound of formula I, stated in Claim 1, or an acid addition or quaternary ammonium salt thereof, which comprises reacting a compound of formula II,



II

in which R_1 is as defined above, and

R_5 is chlorine, bromine or $-OSO_2R_7$, in which

R_7 is alkyl or aryl,

with a compound of formula III,

$$HS-(CH_2)_m-R_2 \qquad III$$

in which m and R_2 are as defined above.

5. The steps, features, compositions and compounds referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations or any two or more of said steps or features.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 79 10 5421

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	GB - A - 1 312 148 (BIOCHEMIE) * Claims * --	1,3,5
	THE JOURNAL OF ANTIBIOTICS, vol. XXIX, no. 9, published September 1976, pages 915-922 Tokyo, JP. H. EGGER et al.: "New pleuromutilin derivatives with enhanced antimicrobial activity. I. Synthesis" * Page 917, formula 1-58; table I, compounds 23-35,58; pages 919-920, Method D * --	1,4,5
	THE JOURNAL OF ANTIBIOTICS, vol. XXIX, no. 9, published September 1976, pages 923-927 Tokyo, JP. H. EGGER et al.: "New pleuromutilin derivatives with enhanced antimicrobial activity. II. Structure-activity correlations" * Page 923, formula 1-58; page 920, table I, compounds 23-35, 58; page 926 * ----	1,3,5

CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)

C 07 D 521/00
A 61 K 31/00//
C 07 D 249/12
249/14
207/22
233/84
235/28
239/56
207/36
277/16
239/38
237/18
239/36
277/74
~~401/04~~

TECHNICAL FIELDS SEARCHED (Int.Cl. ³)

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	31-03-1980	NUYTS

EPO Form 1503.1 06.78

European Patent Office

EUROPEAN SEARCH REPORT

Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	C 07 D 235/06 285/12
			TECHNICAL FIELDS SEARCHED (Int. Cl. ³)